DESIGN, SYNTHESIS, AND BIOLOGICAL EVALUATION OF CHLOROACETYL DERIVATIVES OF 2-METHOXYESTRADIOL AND ABIRATERONE

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Introduction

As a cheap and affordable compound dichloroacetate (DCA) with studied pharmacological effects (fig.1) DCA immediately turned out to be among the promising anticancer drugs. Despite this, interest in drugs based on dichloroacetate is not waning, since the effect of DCA is selective with respect to tumor cells, in which reverse metabolism prevails, and its effect on normal cells is minimal. Also methoxyestradiol (ME) and abiraterone(ABT) are actively used now as anticancer drugs.

Purpose of the study

Synthesis of a number of compounds containing one or more dichloroacetate moieties covalently linked to a carrier via a biodegradable linker. To overcome the metabolic instability of the anticancer agents 2-methoxyestradiol and abiraterone and increase their activity

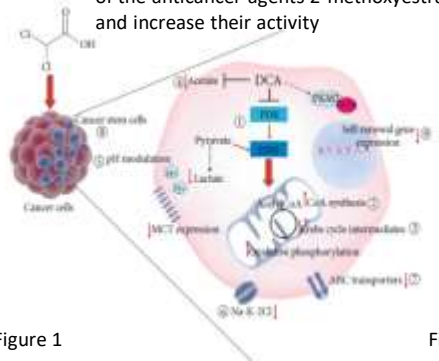
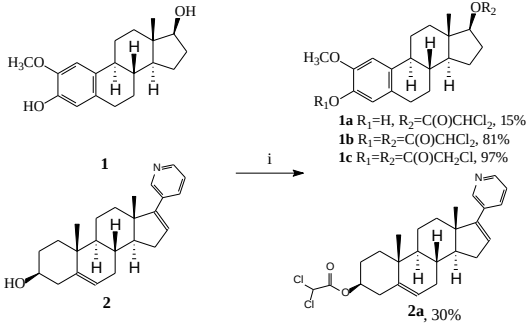


Figure 1

Synthesis



Reagents and conditions: i) $Cl_2CHC(O)Cl$ (for 1a, 1b and 2a) or $ClCH_2C(O)Cl$ (for 1c), 4-DMAP, CH_2Cl_2, STP, 24 hours.

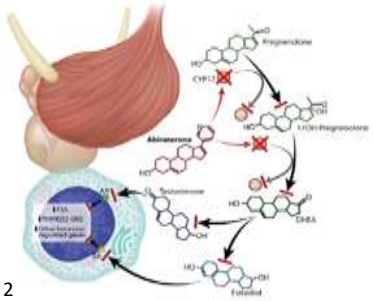


Figure 2

Results

Compound	Cytotoxicity, EC_{50} (μM)	
	MCF-7	HCT-116
1	1.2	n.d.[1]
1a	17.9	n.d.[1]
1b	2.7	n.d.[1]
1c	1.5	n.d.[1]
2	58.6	32.0
2a	44.9	33.5

Conclusion

DCA modification increased cytotoxic activity of abirterone, but worsened the activity of ME. However MCA modification of ME increased microtubule depolymerization effect. Thus, further investigation of both MCA and DCA makes sense.

Literature

[1] Lozinskaya, N. A.; Maximova, N. A.; Bazanov, D. R.; Sosonyuk, S. E.; Wobith, B.; Zefirov, N. A.; Kharitonashvili, E. V; Zefirova, O. N.; Kuznetsov, S. A.; Proskurnina, M. V. Synthesis and Biotesting of New Carrier Prodrugs of 2-Methoxyestradiol. *Mendeleev Communications.*, **2020**, *30* (1), 7–9. https://doi.org/10.1016/j.mencom.2020.01.002.